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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 451/14, 451/04, 453/02 C07D 498/08, A61K 31/47 A61K 31/535 // (C07D 498/08 C07D 265/00, 221/00)	A1	**(11) International Publication Number:** WO 91/17161 **(43) International Publication Date:** 14 November 1991 (14.11.91)

(21) International Application Number: PCT/GB91/00636

(22) International Filing Date: 22 April 1991 (22.04.91)

(30) Priority data:
9009542.3 27 April 1990 (27.04.90) GB

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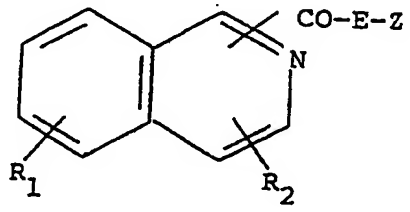
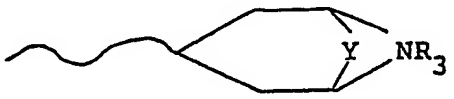
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

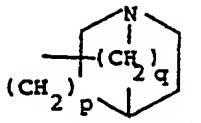
(54) Title: ISOQUINOLINE AMIDES AND ESTERS AS 5 HT3 RECEPTOR ANTAGONISTS



(I)



(a)



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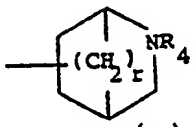

(c)

(57) Abstract

Isoquinoline derivatives (I) having 5-HT_3 receptor antagonist activity, a process for their preparation and their use as pharmaceuticals. In formula (I) E is NH or O, R_1 is hydrogen, halogen, alkyl, alkoxy, hydroxy or nitro; Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c) wherein; p is 1 or 2; q is 1 to 3; r is 1 to 3; R3 or R_4 is hydrogen or alkyl, and Y is a group $-CH_2-X-CH_2-$ wherein X is $-CH_2-$, oxygen, sulphur or X is a bond; and (I) when the group CO-E-Z is in the 1-position and either R_2 is in the 3-position and is hydrogen, alkyl, or alkoxy, or R_2 is in the 4-position and is hydrogen CF3, alkyl, acyl, acylamino (substituted) phenyl or (substituted) amino, (substituted) aminocarbonyl or (substituted) aminosulphonyl; (II) the group CO-E-Z- is in the 3-position and either R_2 is in the 1-position and is hydrogen, alkyl or alkoxy or R_2 is in the 4-position and is hydrogen or alkoxy.

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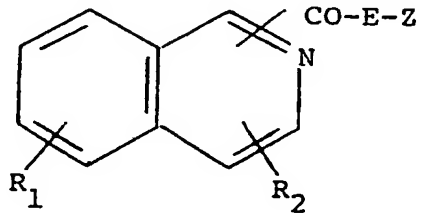
ISOQUINOLINE AMIDES AND ESTERS AS 5-HT_3 RECEPTOR ANTAGONISTS.

This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

GB 2145416A (Sandoz Ltd) describes a group of naphthylene, chromene and quinoline derivatives with saturated azabicyclic side chains, and having 5-HT_3 receptor antagonist activity.

A class of structurally distinct compounds having an isoquinoline moiety, has now been discovered. These compounds have 5-HT_3 receptor antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

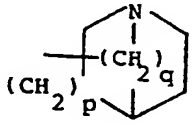
wherein

E is NH or O,

R_1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy or nitro;

Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c):

(a)



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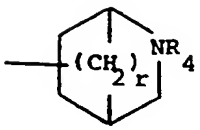


(c)

wherein

p is 1 or 2; q is 1 to 3; r is 1 to 3;

R_3 or R_4 is hydrogen or C_{1-4} alkyl, and Y is a group $-CH_2-X-CH_2-$ wherein X is $-CH_2-$, oxygen, sulphur or X is a bond; and

i) the group CO-E-Z is in the 1-position and either R_2 is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_2 is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

ii) the group CO-E-Z is in the 3-position and either R_2 is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_2 is in the 4-position and is hydrogen or C_{1-6} alkoxy;

having 5-HT_3 receptor antagonist activity.

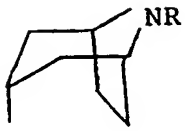
Suitable examples of the group R_1 include hydrogen, bromo, chloro, methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, methoxy, ethoxy, n- and iso-propoxy, and n-, iso-, sec- and tert-butoxy.

Suitable examples of Z are described in the art relating to 5-HT_3 receptor antagonists, ie. as follows:

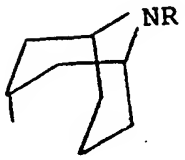
i) GB 2125398A (Sandoz Limited)
ii) GB 2152049A (Sandoz Limited)
iii) EP-A-215545 (Beecham Group p.l.c.)
iv) EP-A-214772 (Beecham Group p.l.c.)
v) EP-A-377967 (Beecham Group p.l.c.)
vi) EP-A-358903 (Dianippon Pharmaceutical Co. Ltd.)

Particular side chains of interest are depicted thus:

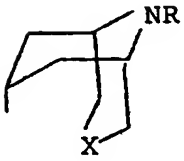
Tropane



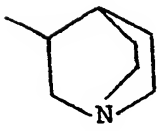
Granatane



Oxa/thia-granatane

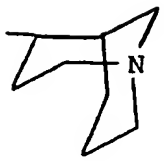


Quinuclidine

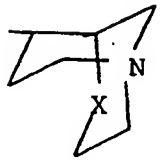


Isoquinuclidine

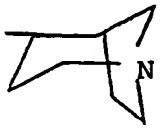
Isogranatane



Oxa/thia-isogranatane



Isotropane



or

wherein
R is hydrogen or methyl; and X is oxygen or sulphur.

Side chains Z of particular interest include tropane and oxagranatane, where R is methyl.

E is preferably NH.

When the group CO-E-Z is in the 1-position suitable examples of the group R_2 when in the 4-position, include the following groups; hydrogen, chloro, bromo, methyl, ethyl, amino, methylamino, dimethylamino, phenyl, C_{1-4} alkanoylamino such as formylamino, acetylamino, propionylamino, n- and iso-butyrylamino, aminosulphonyl, and amino and aminosulphonyl optionally substituted by one or

two methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl or phenyl groups; nitro, methoxy, ethoxy, n- and iso-propoxy, methylthio, ethylthio, n- and iso-propylthio, hydroxy, methylsulphonyl and ethylsulphonyl or when R_2 is in the 3-position suitable examples, include the following groups, hydrogen, methyl, ethyl, n- or iso-propyl, methoxy, and ethoxy.

When the group CO-E-Z is in the 3-position, suitable examples of the group R_2 when in the 1-position, include the groups hydrogen, methyl, ethyl, n- or iso- propyl, methoxy and ethoxy, or when R_2 is in the 4-position, suitable examples include the following groups; hydrogen, methoxy and ethoxy.

Preferred R_2 groups, in any of the positions specified above, include hydrogen, methyl and methoxy. R_2 is preferably in the 1-position.

For the avoidance of doubt, all alkyl and alkyl containing moieties are straight chained or branched.

Examples of R_3/R_4 when alkyl are methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, preferably methyl.

Preferably p, q and r are 1 or 2.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, lactic, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_a-T wherein R_a is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_a include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl, preferably methyl. Suitable examples of T include halide such as chloride, bromide and iodide.

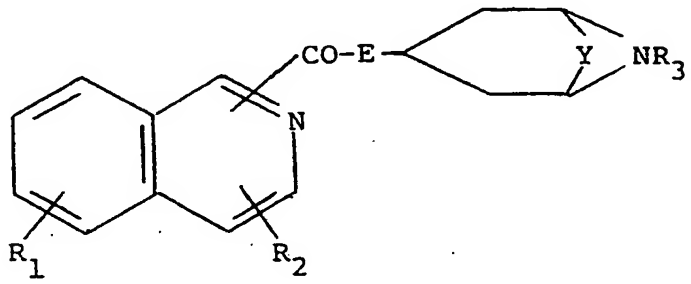
Examples of pharmaceutically acceptable salts of compounds of formula (I) also include internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that the isoquinoline nucleus in compounds of formula (I) may adopt an endo or exo configuration with respect to Z. The endo configuration is preferred.

A group of compounds within formula (I) is of formula (II):

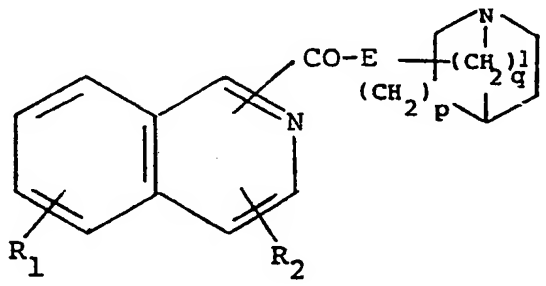


(II)

wherein the variables are as defined in formula (I).

Examples of the variables and preferred variables are as so described for corresponding variables in relation to formula (I).

A further group of compounds within formula (I) is of formula (III):

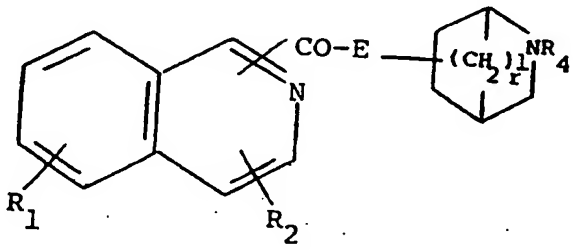


(III)

wherein q^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are as so described for the corresponding variables in formula (I).

There is a further group of compounds within formula (I) of formula (IV):

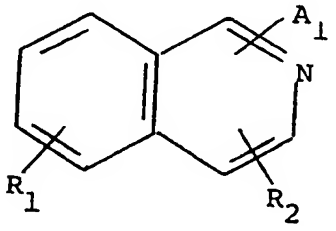


(IV)

wherein r^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are so described as the corresponding variables in formula (I).

The invention also provides a process for the preparation of a compound of formula (I) which process comprises reacting a compound of formula (V):



(V)

with a compound of formula A_2-Z' wherein Z' is Z as defined in formula (I) wherein R_3 and R_4 are replaced by R_3' and

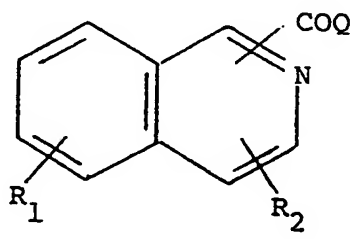
R_4', A_1 and A_2 are moieties which react together to form an amide or ester linkage and R_3' and R_4' are R_3 and R_4 respectively, as defined in formula (I) or a hydrogenolysable protecting group; and thereafter as desired or necessary, converting R_3', or R_4' when other than R_3 or R_4 respectively, to R_3 and R_4 respectively, and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

Suitable values of A_1 and A_2 are, for example, as described in the aforementioned patent publications. For example, A_1 may be an actived carbonyl function such as an acid chloride or N-hydroxysuccinmide ester and A_2 may be an amino group, when E in formula (I) is NH.

Intermediates of the formula (V) are generally known or are prepared by analogous methods to those used for structurally related known compounds.

Intermediates of formula A_2-Z' may be prepared from the corresponding exocyclic keto derivative of the azabicyclic side chain, prepared by condensation methods, often using a substituted piperidine, as described in the aforementioned patent references.

In a particular aspect, the invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (VI):



(VI)

with a compound of formula HJ-Z', or when J is oxygen, an active derivative thereof, wherein J is oxygen or NH, Q is a leaving group; R_3' and R_4' respectively is R_3 and R_4 respectively, as defined, or a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting R_3' or R_4', when other than R_3 or R_4, to R_3, or R_4 respectively, and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q, displaceable by a nucleophile, include halogen such as chloro and bromo, C_{1-4} alkoxy, such as CH_3O and C_2H_5O-, PhO-, or activated hydrocarbyloxy, such as Cl_5C_6O- or COQ forms a mixed anhydride, so that Q is carboxylic acyloxy.

If a group Q is a halide or COQ forms a mixed anhydride, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0^o-100^oC, in particular 10-80^oC are suitable.

If a group Q is C_{1-4} alkoxy, phenoxy or activated hydrocarbyloxy, or activated ester, such as N-hydroxysuccinimide, then the reaction is preferably carried out in an inert polar solvent, such as toluene or dimethylformamide. It is also preferred that the group Q is Cl_3CO- and that the reaction is carried out in toluene at

reflux temperature.

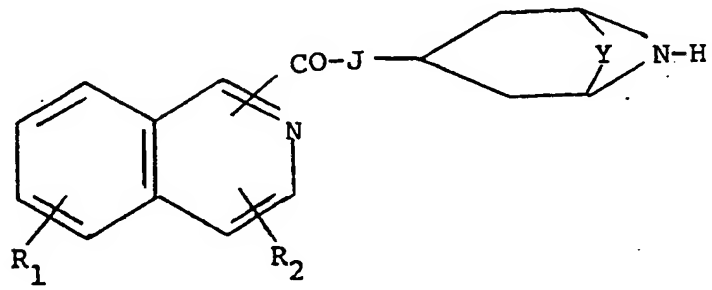
If a group Q is hydroxy, then the reaction is generally carried out in an inert non-hydroxylic solvent, such as dichloromethane, THF or DMF optionally in the presence of a dehydrating agent such as a carbodiimide, for example dicyclohexylcarbodiimide, optionally in the presence of N-hydroxysuccinimide. The reaction may be carried out at any non-extreme temperature, such as -10 to 100°C, for example, 0 to 80°C. Generally, higher reaction temperatures are employed with less active compounds whereas lower temperatures are employed with the more active compounds.

If a group Q is carboxylic acyloxy, then the reaction is preferably carried in substantially the same manner as the reaction when Q_1 is halide. Suitable examples of acyloxy leaving groups include C_{1-4} alkanoyloxy and C_{1-4} alkoxycarbonyloxy, in which case the reaction is preferably carried out in an inert solvent, such as dichloromethane, at a non-extreme temperature for example ambient temperatures in the presence of an acid acceptor, such as triethylamine. C_{1-4} alkoxycarbonyloxy leaving groups may be generated <u>in situ</u> by treatment of the corresponding compound wherein Q is hydroxy with a C_{1-4} alkyl chloroformate.

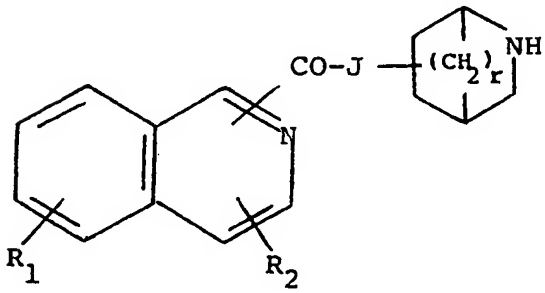
If a group Q is activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as dimethylformamide. It is also preferred that the activated hydrocarbyloxy group is a pentachlorophenyl ester and that the reaction is carried out at ambient temperature.

When J is O the compound of formula HJ-Z', may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

R_3' and R_4' when other than R_3 and R_4 respectively, may be a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo, C_{1-4} alkoxy and C_{1-4} alkyl. Such benzyl groups may, for example, be removed, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (VII) or (VIII) respectively:



(VII)



(VIII)

wherein the variables are as hereinbefore defined.

This invention also provides a further process for the preparation of a compound of the formula (I) wherein Z is a) or c) or a pharmaceutically acceptable salt thereof, which comprises N-alkylating a compound of formula (VII) or (VIII)

respectively, and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I).

In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (VII) or (VIII) respectively, by a group R_3 or R_4 respectively as hereinbefore defined. This may be achieved by reaction with a compound R_3Q_3 or R_4Q_3 as necessary wherein R_3 and R_4 are as hereinbefore defined and Q_3 is a leaving group.

Suitable values for Q_3 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$.

Favoured values for Q_3 include Cl, Br and I.

The reaction may be carried out under conventional alkylation conditions, for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above.

Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions.

Interconverting R_3 and R_4 respectively in the compound of the formula (VII), or (VIII) respectively, before coupling with the compound of the formula (VI) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R_3 or R_4 interconversions.

It is often convenient in the preparation of such a compound of formula (VII) or (VIII) to prepare the corresponding

compound wherein the methylene group is replaced by -CO-, or for R_3 or R_4 is methyl, where the methyl group is replaced by alkoxycarbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (VII) or (VIII) respectively.

The compounds of formula (VI) are known or are preparable analogously to, or routinely from, known isoquinoline compounds.

It will be realised that in the compounds of the formula (I) having a tropane, granatane or oxa/thia-granatane side chain, the -COE- linkage has an endo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo isomer may if desired by synthesised from the corresponding endo form of the compound of the formula (II). Corresponding geometric isomeric pairs are possible for the isoquinuclidine, isogranatane, oxa/thia-isogranatane and isotropane side chains.

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally. The acid addition salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT_3 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain;

emesis, includes in particular that of preventing vomiting and nausea associated with cancer therapy, and motion sickness. Examples of such cancer therapy include that using cytotoxic agents, such as cisplatin, doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, senile dementia and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrohea.

5-HT_3 receptor antagonists may also be of potential use in the treatment of obesity and/or arrhythmia.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants

include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large

quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain

0.05 to 1000mg for example 0.1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a pharmaceutical composition for use in the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders which composition comprises an effect non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The invention further provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The following Examples illustrate the preparation of compounds of formula (I), the following descriptions illustrate the preparation of intermediates.

Description 1

4-Methyl-1-isoquinoline carboxaldehyde (D1)

To a solution of 1,4-dimethyl isoquinoline (9.46g) (K.C. Agrawal, P.D. Mooney and A. C. Sartorelli, J. Med. Chem., 1976, 19, 970) in 1,4-dioxane (250 ml) was added selenium dioxide (6.65g) and the mixture heated under reflux, under an atmosphere of nitrogen, for 4h. After allowing the reaction mixture to cool to room temperature, the precipitated selenium was removed by filtration and the filtrate concentrated to dryness. The residue was purified by flash chromatography on silica gel, using light petroleum ether (bp 60-80°C) and diethyl ether (up to 20% v/v) as eluent, to afford the aldehyde (D1) (3.78g) as a tan solid. Mp. 61-63°.

M.S. M^+ 171

n.m.r. ($CDCl_3$, 250 MHz)

δ	2.74	(s, 3H)
	7.71-7.87	(m, 2H)
	8.05	(d, 1H)
	8.63	(s, 1H)
	9.38	(d, 1H)
	10.35	(s, 1H)

Description 2

4-Methyl-1-isoquinoline carboxylic acid (D2)

To an aqueous solution of silver oxide (prepared by the addition of silver nitrate (5g) in water (10 ml) to a stirred solution of sodium hydroxide (2.40g) in water (10 ml)) was added, at 0°C, 4-methyl-1-isoquinoline

carboxaldehyde (D.1) (2.50g), in portions. The reaction mixture was stirred at ambient temperatures overnight. The silver suspension was removed by filtration and washed with hot water (3x5 ml). The combined filtrate and washings were acidified with conc. HCl and extracted with chloroform (3x50 ml). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford the title compound (D2) (980 mg) as a beige solid mp. 155-57°.

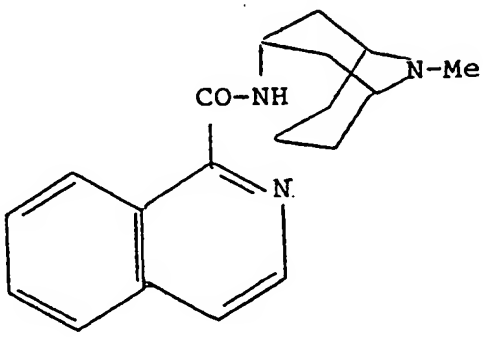
M.S. MH^+ 188

n.m.r. ($CDCl_3$, 250 MHz)

δ	2.75	(s, 3H)
	7.79-7.92	(m, 2H)
	8.07	(d, 1H)
	8.43	(s, 1H)
	9.67	(d, 1H)
	10.58	(bs, 1H)

Example 1

endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)isoquinolin-1-carboxamide (E1)



(E1)

A solution of isoquinolin-1-carboxylic acid (2g), N-hydroxysuccinimide (1.5g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.6g) was stirred in dry DMF (50ml) at room temperature for 4 hours. The reaction mixture was cooled at 0°C, endo-N-(9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (2g) in CH_2Cl_2 (30ml) was added and the mixture stirred at room temperature overnight. The solvent was removed and the residue dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried and concentrated. The residue was recrystallised from Ethyl acetate and petrol (Bpt. range 60-80°C), to give the title compound (2.4g).

m.p. 155-157°C.

Examples 2 to 6

The following compounds are prepared analogously to example 1 or as hereinbefore described.

Example	Point of attachment of CO-NH-Z_1	R_2^1	Z_1
E2	1	H	N-methyltropane
E3	3	H	N-methyltropane
E4	1	H	quinuclidin-3-yl
E5	1	4-CH_3	N-methyltropane
E6	1	H	N-methyloxagranatane

Example 2

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)isoquinolin-1-carboxamide (E2)

mp 87-88°

^{1}H-NMR ($CDCl_3$)

δ	9.67	(d, 1H)
	8.75	(d, 1H)
	8.48	(d, 1H)
	7.9-7.6	(m, 4H)
	4.42-4.28	(m, 1H)
	3.25	(brs, 2H)
	2.42-1.70	(m, IIH including 2.35, s, 3H)

Example 3

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-isoquinolin-3-carboxamide (E3)

mp 133-136°

^{1}H-NMR ($CDCl_3$)

δ	9.19	(s, 1H)
	8.85	(brd, 1H)
	8.60	(s, 1H)
	8.10-7.95	(m, 2H)
	7.80-7.65	(m, 2H)
	4.36	(dt, 1H)
	3.25	(brs, 2H)
	2.44-1.95	(m, 9H including 2.36,s, 3H)
	1.85	(brd, 2H)

Example 4

N-(Quinuclidin-3-yl)isoquinolin-1-carboxamide(E4)

mp 115-117°

^{1}H-NMR ($CDCl_3$)

δ	9.62	(d, 1h)
	8.51-8.40	(m, 2h)
	7.9-7.62	(m, 4h)
	4.35-4.15	(m, 1h)
	3.58-3.41	(m, 1h)
	3.10-2.82	(m, 4h)
	2.75	(dd, 1h)
	2.41-1.5	(m, 5h)

Example 5

endo-N-(9-Methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-yl)-isoquinolin-1-carboxamide (E5)

mp 148-150°

^{1}H-NMR ($CDCl_3$)

δ	10.03	(brd, 1H)
	9.42	(d, 1H)
	8.50	(d, 1H)
	7.9-7.62	(m, 4H)
	4.88-4.72	(m, 1H)
	4.10	(d, 2H)
	3.68	(d, 2H)
	2.75	(brs, 2H)
	2.67-2.50	(m, 5H including 2.60, s, 3H)
	1.60	(d, 2H)

Example 6

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-methyl-1-isoquinolin-1-carboxamide hydrochloride (E6)

A solution of 4-methyl-1-isoquinoline carboxylic acid (500 mg) (D2) and N-hydroxy succinimide (368 mg) in dry DMF (15 ml) was stirred under an atmosphere of nitrogen at ambient temperatures for 30 min. 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide (768 mg) was added in one portion and stirring continued for 1h. The reaction mixture was cooled to 0°C and a solution of endo-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (374 mg) in DMF (5 ml) was added dropwise and stirring continued for 20h at ambient temperatures. The solvent was removed in vacuo and the residue partitioned between chloroform (50 ml) and 10% aq. NaOH (5 ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel, using chloroform and ethanol (up to 10% v/v) as the eluent to afford an oil. Treatment with ethanolic HCl gave the title compound (200 mg) as a pale yellow solid. m.p. 140-43°.

M.S. M^+ 309 (Free base)

^{1}H-NMR (d_4-MeOH, 250 MHz)

δ	2.33-2.52	(m, 5H)
	2.59-2.65	(m, 2H)
	2.84	(s, 3H)
	2.92	(s, 3H)
	3.02	(d, 1H)
	3.89-4.06	(m, 2H)
	4.40-4.53	(m, 1H)
	8.10	(t, 1H)
	8.30	(t, 1H)
	8.44-8.60	(m, 3H)

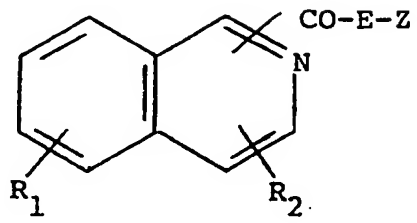
5-HT_3 Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) is then determined.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

E is NH or O,

R_1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy or nitro;

Z is an azacyclic or azabicyclic side chain; and

i) the group CO-E-Z is in the 1-position and either R_2 is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_2 is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

ii) the group CO-E-Z is in the 3-position and either R_2 is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_2 is in the 4-position and is hydrogen or C_{1-6} alkoxy;

having $5\text{-}HT_3$ receptor antagonist activity.

2. A compound according to claim 1 wherein E is NH.

3. A compound according to claim 1 or 2 wherein CO-E-Z is in the 1-position.

4. A compound according to any one of claims 1 to 3 wherein R_1 is hydrogen.

5. A compound according to any one of claims 1 to 4 wherein Z is tropane, granatane, oxa/thia-granatane, quinuclidine, isoquinuclidine, isogranatane, oxa/thia-isogranatane or isotropane.

6. endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)isoquinolin-1-carboxamide.

7. endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-isoquinolin-1-carboxamide.

8. endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-isoquinolin-3-carboxamide.

9. N-(Quinuclidin-3-yl)isoquinolin-1-carboxamide.

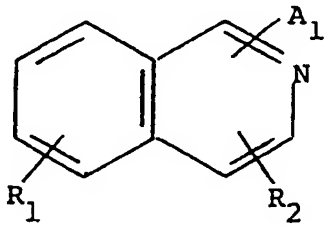
10. endo-N-(9-Methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-yl)-isoquinolin-1-carboxamide.

11. endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-methyl-1-isoquinolin-1-carboxamide.

12. A pharmaceutically acceptable salt of a compound according to any one of claims 6 to 11.

13. A compound according to claim 1 substantially as defined herein with reference to the Examples.

14. A process for the preparation of a compound according to claim 1, which process comprises reacting a compound of formula (V):



(V)

with a compound of formula A_2-Z' wherein Z' is Z as defined in claim 1 wherein R_3 and R_4 are replaced by R_3' and R_4', A_1 and A_2 are moieties which react together to form an amide or ester linkage and R_3' and R_4' are R_3 and R_4 respectively, as defined in claim 1, or a hydrogenolysable protecting group; and thereafter as desired or necessary, converting R_3', or R_4' when other than R_3 or R_4 respectively, to R_3 and R_4 respectively, and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

15. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

16. A method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound according to claim 1.

17. A compound according to any one of claims 1 to 13 for use as an active therapeutic substance.

18. A compound according to any one of claims 1 to 13 for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

19. The use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/00636

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 451/14, 451/04, 453/02, 498/08, A 61 K 31/47, A 61 K 31/535// (C 07 D 498/08, 265:00,221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 451/00, C 07 D 453/00, C 07 D 498/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0189002 (SANDOZ) 30 July 1986 see claims 1,2,3 --	1,18
A	WO, A, 8400166 (SANDOZ) 19 January 1984 see claims 1,2; page 44, line 9 - page 47, line 10 cited in the application --	1,18
A	WO, A, 8401151 (BEECHAM) 29 March 1984 see claims 1,2; page 41 - page 44; page 29, lines 20-28 --	1,18
A	EP, A, 0200444 (BEECHAM) 5 November 1986 see claim 1; page 20, line 34 - page 21, line 16 -- ./.	1,18

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9th July 1991	02.09.91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	EP, A, 0041817 (BEECHAM) 16 December 1981 see claim 1; page 25, lines 22-30 ----------	1,18

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 16, because they relate to subject matter not required to be searched by this Authority, namely:

Please see RULE 39.1(iv) - PCT

Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9100636 SA 46790

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0189002	30-07-86	DE-A- 3446484	03-07-86
		DE-A- 3531281	12-03-87
		DE-A- 3531282	12-03-87
		AU-B- 595172	29-03-90
		AU-A- 5139685	31-07-86
		JP-A- 2237920	20-09-90
		JP-A- 61152628	11-07-86
WO-A- 8400166	19-01-84	AT-B- 391136	27-08-90
		AU-B- 570002	03-03-88
		AU-A- 1628683	05-01-84
		AU-B- 603399	15-11-90
		AU-A- 8243487	28-04-88
		CH-A- 669792	14-04-89
		CH-A- 669954	28-04-89
		DE-A- 3322574	29-12-83
		DE-A- 3348331	31-08-89
		DE-A- 3348332	07-09-89
		DE-A- 3348333	24-08-89
		DE-A- 3348334	31-08-89
		FR-A,B 2531083	03-02-84
		GB-A,B 2125398	07-03-84
		GB-A,B 2166726	14-05-86
		GB-A,B 2166727	14-05-86
		GB-A,B 2166728	14-05-86
		NL-A- 8302253	16-01-84
		SE-B- 463210	22-10-90
		SE-A- 8303651	30-12-83
		US-A- 4803199	07-02-89
		US-A- 4910207	20-03-90
		US-A- 5017582	21-05-91
		BE-A- 897117	23-12-83
		CA-A,C 1257870	25-07-89
		JP-A- 59067284	16-04-84
		JP-A- 59036675	28-02-84
		US-A- 4789673	06-12-88
WO-A- 8401151	29-03-84	EP-A- 0126087	28-11-84

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9100636 SA 46790

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0200444	05-11-86	AU-B- 594670	15-03-90
		AU-A- 5657986	06-11-86
		JP-A- 61275276	05-12-86
		US-A- 4937247	26-06-90
		US-A- 4886808	12-12-89
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